REMARKS

Claims 1, 11, 36, 42, 43, 82-88, 90-96 are pending in the instant application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance.

I. The Rejection of Claims 1, 11, 36, 42-43, 82-88, and 90-96 under 35 U.S.C. § 103

Claims 1, 11, 36, 42-43, 82-88, and 90-96 stand rejected under 35 U.S.C. § 103 as being unpatentable over Wilson *et al.* (*PNAS* 96: 12833-12838, 1999) in view of Cao *et al.* (*Mol. Microbiol.* 45: 1267-1276, 2002) for the reasons of record. This rejection is respectfully traversed for the reasons of record and further for the reasons stated below.

The Advisory Action asserts: "Applicants urge that Wilson et al., in view of Cao et al., do not teach the subinhibitory amount limitation. However, it is the position of the Office that Wilson et al. teach concentrations of 0.2 µg or 1 lµg [sic] of INH per ml, growth occurs and the bacteria is not killed as evidenced by the INH-induced expression profiles. Thus, Wilson et al. meets the sub-inhibitory limitation of the claims." Applicants disagree on the ground that the facts in Wilson *et al.* do not support the Office's conclusion.

In the Amendment of June 28, 2010, Applicants pointed out that the Office has mischaracterized Wilson *et al.* Wilson *et al.* first grow the *M. tuberculosis* strain to early log phase before the addition of INH at a concentration of 0.2 µg or 1 µg per ml. The Office has incorrectly concluded that INH was added at the beginning of growth and thus present during growth to early log phase, which it was not. Wilson *et al.* state the following on page 12834 under "Growth and Drug Treatment of *M. tuberculosis* Strains" in the second paragraph:

> Cultures for experimental treatment were initiated by diluting a frozen stock inoculum 1:200 into fresh 7H9 media in vented, screw-cap, tissue culture flasks and grown to early log phase (0.15-0.3 OD_{600}) with shaking (80 rpm) in a 5% CO_2 atmosphere at 37°C. Drug treatment was begun by adding filtered stock solutions of INH (1 mg/ml, Sigma) or ethionamide (25 mg/ml, Sigma) to achieve the following final concentrations: 0.2 µg/ml or 1 µg/ml for INH and 5 µg/ml or 20 µg/ml for ethionamide. Upon completion of the predetermined duration of drug treatment, the bacteria were harvested by centrifugation, and the pellets were rapidly frozen in crushed dry ice and stored at -80°C for RNA isolation.

Applicants respectfully request that the Office acknowledge its mischaracterization of Wilson *et al.*

The Advisory Action also asserts: "Furthermore. it is the position of the Office that differences in concentration or temperature will not support the patentability of subject matter

encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454,456, 105 USPQ 233, 235 (CCPA 1955)." Applicants disagree on the ground that the Office's reliance on *In re Aller* is misplaced.

It is well known in the art that the minimum inhibitory concentration of INH is 0.02 µg of INH per ml. Consequently, 0.02 µg of INH per ml is **NOT** an example of a subinhibitory amount. Wilson *et al.* use isoniazid (INH) at concentrations **above** the minimum inhibitory concentration of INH. Applicants use subinhibitory amounts that are **below** the minimum inhibitory concentration.

In re Aller held that "it's obvious to routinely experiment and optimize" according to the facts of *In re Aller*. The claimed process in *In re Aller* resulted from experimentally varying the different factors of the prior art process to optimize the reaction conditions. One skilled in the art would recognize that optimization of the inhibitory range of an antimicrobial compound would involve concentrations above the minimum inhibitory concentration, not sub-inhibitory concentrations. In the instant application, Applicants have not optimized the inhibitory range of an antimicrobial compound, but rather use sub-inhibitory concentrations, which do not fall within or overlap concentrations above the minimum inhibitory concentration. Applicants submit that *In re Aller* is not relevant to the instant application.

Applicants submit that the claimed methods produce unexpected results. Applicants have shown that the use of sub-inhibitory amounts of an antimicrobial compound result in the ability to more readily identify primary effects of the antimicrobial compound on genes of a bacterial cell and reduce secondary effects on other genes that can result from using high inhibitor concentrations of the compound. The use of sub-inhibitory concentrations consequently slows the action of the compounds, and limits the expression of genes that are correlated to secondary effects, allowing a predominance of expressed nucleic acids that correlate with the activity of the antimicrobial compound, which is related directly, and primarily, with its mode of action on the cell. In contrast, gene expression responses to concentrations of an inhibitor above its minimum inhibitory concentration cause a broader effect on cellular processes by the inhibition of secondary targets within the cell, as well as by downstream effects that result from inhibition of the primary target, thereby giving much more complex response patterns. Applicants' submit that their results exhibit a superior advantage that a person skilled in the art would have found surprising and unexpected.

For the foregoing reasons, Applicants submit that the rejections under 35 U.S.C. § 103

have been overcome and respectfully request reconsideration and withdrawal of the rejections.

II. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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